REMARKS

FORMAL MATTERS:

With entry of this paper, claims 1, 7, 8, 12-16, 25, and 28-34 are pending and stand as rejected by the Examiner.

Claims 2-6, 9-11, 17-24, 26, 27, 35-38, 41-46, 49-50, 57 and 58 where previously canceled.

Claims 51-54 are canceled with entry of this paper.

Claims 39, 40, 47, 48, 55, 56, and 59-62 stand as withdrawn.

Claims 1, 16, 25, and 34 have been amended. Withdrawn claims 39, 40, 47-48, 55 and 59 have been amended for consistency with prosecuted claims. Applicants respectfully request rejoinder of withdrawn claims for reasons presented below.

Amendment to the claims is made to clarify the nature of the invention by removing inadvertent text identified by the Examiner, or correcting grammatical inconsistencies. Support for the amendments may be found throughout Applicants' specification, for example in paragraphs [0046], [0052] and [0055], and Figures 2-4.

No new matter is added. The claims raise no new issues, but rather place the claims in better form for allowance. Entry of the amendments is thus respectfully requested.

Applicants respectfully request reconsideration of the pending rejections in light of the claim amendments and remarks presented with this paper.

OBVIOUSNESS-TYPE DOUBLE PATENTING

Claims 1 , 4-8, 12- 16, 25 and 28-35 stand provisionaily rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1 - 14 of copending Application No. 11/193,3 18. The rejection is provisional because the allegedly conflicting claims have not been patented. Applicants request that the rejection be held in abeyance until the claims at issue are allowed and an actual obviousness-type double patenting rejection can be presented.

Similarly, claims l, 4, 5, 9, 8, 12-16, 25 and 28-38 stand provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 3-6, 8-11, 13-17, and 20-52 of copending Application No. 10/678,760. The rejection is provisional because the allegedly conflicting claims have not been patented. Applicants request that the rejection be held in abeyance until the claims at issue are allowed an actual obviousness-type double patenting rejection can be presented.

REJECTIONS UNDER §102

Claims 1, 7-8, 14, and 16 are rejected under 35 U.S.C. 102(b) as being anticipated by Lee *et al.*, (PCT Publication No. WO 01/40511 A2, published 7 June, 2001). This rejection is respectfully traversed as applied, and as it may be applied to the pending claims.

In order to anticipate Applicants' invention, a prior art document must contain all of the elements and limitations of the Applicants' rejected claim(s). There must be no difference between the claimed invention and the reference disclosure, as viewed by a person of ordinary skill in the field of the invention. *Scripps Clinic & Research Found. v. Genentech, Inc.*, 18 USPQ2d 1001, 1010 (Fed. Cir. 1991).

Lee fails to discloses a probe immobilized to an electrode in the manner required by claim 1 such that in the absence of target-probe hybridization a redox moiety of the probe is at a first position, and in the presence of target-probe hybridization the redox

moiety is at a second position, where *the second position provides more efficient electron transfer between the redox moiety and the electrode than the first position.*[1] Stated differently, when the immobilized probe of the detector of claim 1 is *hybridized* to a target, the position of the redox moiety in relation to the electrode provides more efficient electron transfer than when the probe *is not hybridized* to a target. Thus, when the redox moiety is in the second position in the presence of target-probe hybridization, it necessarily provides for a greater signal relative than when the redox moiety is in the first position in the absence of hybridization. For the convenience and brevity in this response, this element of claim 1 is referred to as "signal on" configuration.

The Office Action refers to Lee page 12, lines 5-9 to support the proposition that the Lee probe carries a redox moiety and has a nucleotide sequence which hybridizes with the target nucleotide sequence. Taken in its entirety, Lee page 12, lines 5-9 reads:

> "In all of these cases, hybrisation (sic) of the probe to the target sequence will result in a change in redox properties as the *relative spacing of the pair of labels* changes. This change can be recorded by taking the electrochemical measurements in the course of the reaction." (Emphasis added.)

When read in the context of the Lee reference as a whole, it is evident that this passage refers to the paragraph immediately preceding the cited passage, which describes hybe-type probes. Hybe-type probes are described in Lee as being a two-part probe system, where two probes each having a label hybridise to the target sequence in close proximity to each other so that the labels are brought into proximity at that time. Applicants respectfully point out that the Applicants' claimed invention is not such a two-part probe system, but rather requires the redox moiety be present on a probe immobilized on detector and in a "signal on" configuration as discussed above.

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[1] The Office Action at page 3 asserts that this element is disclosed in Lee, but points to no portion of Lee in support of this assertion.

Moreover, even if the reference in the cited passage to "all of these cases" refers to probes discussed in all previous paragraphs, i.e., Scorpion ™, TAQMAN ™, Molecular Beacons® and hybe-type probes, the Lee disclosure still fails to reach Applicants' invention. There is no disclosure in Lee of immobilizing any probe on an electrode to provide the "signal on" configuration required by claim 1. Indeed, the whole of Lee discloses detecting hybridization as a result of interaction *between a pair of labels*. The basis for detection of target-probe hybridization in Lee is a change in electrochemical measurements as a result of a redox reaction between a pair of labels (e.g., due to FRET). Lee States:

> Alternatively [to a two-probe/two-label system] the probe may comprise a pair of labels which will undergo a detectable redox reaction when in close proximity to *each other*. (emphasis added)
>
> Lee at p. 11, lines 20-22.

Thus Lee does not teach nor envisage the "signal-on" configuration required by claim 1 because in order to generate a redox reaction-based signal between the two labels, the "molecular beacon" and "scorpion"-type probes, *the labels must be in close proximity to each other*. Thus, according to Lee, the redox signal to be detected is generated when these probes are *not* hybridized to a target. Hybridization of target and probe in these systems separates the pair of labels, preventing the detectable redox reaction sought to be measured. Thus Lee discloses a detection system that is "signal off," not "signal on" as required by Applicants' claims.

Moreover, Lee provides no direction as to how such probes are to be attached to an electrode, or that positioning of a label relative to the electrode is of consequence. As discussed above, it is the contention of Lee that it is label-label proximity that is important in generating a redox event, not label-electrode proximity. There is nothing in Lee that discloses or suggests detecting hybridization as a result of the relative positioning of a redox moiety to an electrode. In contrast, claim 1 relies upon detection target -probe hybridization as a result of ***a change in the distance of a redox moiety from an electrode, where the probe is immobilized to the electrode.*** Therefore, a plain reading of the cited passage cannot be

reasonably construed as referring to a probe immobilized to an electrode and providing for the detection of hybridization to a target sequence according to Applicants' claims: I.e., via a signal generated as a result of more efficient electron transfer due to the positioning of the redox moiety in relation to the electrode, when the probe *is not hybridized* to a target, thereby generating a "signal-on" response.

The Office seeks support for an immobilized probe on a detector by reference to Lee at page 14, line 2.[2] The entire paragraph containing the cited passage reads:

> Depending on the nature of the assay being studied and the detection means being employed, the probe may either be free in solution or immobilized on a support, for instance on an electrode.
>
> Lee at p. 13, line 36 et seq.

Given the numerous types of probe systems disclosed in Lee, and the many possible different configurations that could be used to accomplish immobilization of probes of these systems to an electrode, this disclosure of Lee at best represents a broad genus of soluble probes immobilized on an electrode in a genus of configurations.[3] Again, there is simply no guidance to provide any probe disclosed in Lee in a "signal on" configuration as required by claim 1. As noted above, Lee discloses detecting hybridization as a result a redox reaction *between of a pair of labels*. There is nothing in Lee that discloses or suggests detecting hybridization *as a result of the relative positioning of a redox moiety to an electrode*.

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[2] Applicants acknowledge the citation in the Office Action to Lee p.4, line 35, but submit that there is no mention of a probe immobilized to an electrode in the Lee specification prior to page 14, line 2

[3] It is well-settled that a genus cannot anticipate a species. See, *e.g., In re Petering*, 301 F.2d 676, 133 USPQ 275 (CCPA 1962); MPEP §2131.02.

It is well settled law that in order to anticipate a claim, a reference must be enabling so as to place the claimed invention in the hands of the public.[4] Applicants respectfully reiterate that Lee provides no guidance on how to immobilize a probe to an electrode so as to provide the "signal on" configuration of claim 1. Lee is silent as to how soluble probes are to be modified to render them suitable as immobilized probes. Lee also lacks any discussion whatsoever as to the nature of any contemplated immobilized probe. Certainly there is no teaching in Lee that the Lee probes are attached to an electrode in the manner and orientation claimed as Applicants' invention. Indeed, as previously noted, many of the probes disclosed in Lee require amplification to occur in order for the detection system to work, and further require two labels.

Therefore, Applicants respectfully submit that Lee fails to teach each of Applicants' limitations, and lacks the requisite enablement under 35 U.S.C. 112, first paragraph to be considered prior art against Applicants' claimed invention. Accordingly, Applicants respectfully request the instant rejection be withdrawn.

REJECTIONS UNDER §103

Claims 1 and 12 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lee *et al.*, (PCT Publication No. WO 01/40511 A2, published 7 June, 2001) in view of Egholm *et al.*, (U.S. Patent No. 6,451,588 Bl, issued 17 September, 2002).

This rejection is respectfully traversed.

The Office concedes that Lee is "silent with respect to internal hybridization in the second conformation." The Office proposes combining Egholm to overcome the deficiencies found in Lee. According to the Office, Egholm teaches immobilized nucleic acid probes wherein upon hybridization to the target, the probe comprises internal hybridization, with the added advantage of allowing use of two low-complexity libraries having less that 0.005% of the probes required by a single high-complexity library.

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[4] *See, e.g.,*, ***In re Donohue***, 226 USPQ 619 (Fed. Cir. 1985). ***See also*** See MPEP §§ 201.11 and 706.02.

Establishing a *prima facie* case for obviousness under §103 requires the Office to show, *inter alia*, that the references cited against Applicants teach or suggest all claim limitations of the rejected claim(s). *In re Royka*, 180 USPQ 580 (CCPA 1974); and MPEP §2143.03.

As explained above, Lee fails to disclose a probe immobilized on a detector so as to provide a "signal on" configuration (i.e., the redox moiety is in a position providing more efficient electron transfer than when the probe *is hybridized* to a target than in the absence of hybridization). Egholm fails to cure this deficiency.

Egholm discloses probe systems having two labels. Indeed, when taken in context, the citation from Egholm presented in the Office action illustrates this fact:

> The binding moieties of the present invention are formed by combining *at least a first probe and a second probe in solution.* It is understood that one of the probes may optionally be immobilized on a solid support through an ionic interaction, affinity/receptor nteraction, or covalent linkage (U.S. Pat. No. 5,639,609).
>
> Egholm at Col. 15, lines 38-43.

The two probe/label system is essential to Egholm as the probes discussed use fluorescent labels, such as those depicted in Figure 4 and discussed in Col. 12, lines 1-13 of the Egholm patent. As with Lee, Egholm identifies the proximity of multiple labels as the key to generating a redox event, not the position of a label from an electrode, where the label is bound to an oligonucleotide tethered to the electrode as required by Applicants' claims. Assuming any label presented in Egholm is repositioned in response to hybridization of target and probe sequences, it is the label on the probe in solution that is repositioned, not the label on the probe bound to the electrode, as required by Applicants' claims. Therefore, the proposed combination of Egholm and Lee cannot render Applicants' invention obvious as it fails to teach every limitation of Applicants' claimed

invention. Accordingly, Applicants respectfully request the rejection presented be withdrawn.

Claims 1 and 13 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lee *et al.*, (PCT Publication No. WO 01/40511 A2, published 7 June 2001) in view of Rothberg *et al.*, (U.S. Patent Application Publication No. US 2002/0012930 Al, published 31 January 2002).

The Office concedes that Lee *et al* do not teach loops in the target and the probe in the second conformation (i.e., during hybridization). The Office proposes a combination of Lee and Rothberg renders Applicants' claimed invention obvious. Applicants respectfully disagree.

As explained above, Lee *et al.* fail to teach or suggest all limitations to Applicants' claimed invention, and particularly a probe immobilized on a detector so as to provide a "signal on" configuration (i.e., so that the redox moiety is in a position closer to the electrode in the presence of hybridization than in the absence of hybridization).

Rothberg *et al* is characterized by the Office as disclosing probes hybridized to targets wherein the probe and the target have a loop during hybridization, wherein the hybridized rolling circle probe leaves a loop in the target in the form of the gapped region and a loop in the form of the single stranded portion of the rolling circle template molecule. Rothberg *et al* allegedly disclose the loop in the target has the added advantage of allowing detection of single nucleotide polymorphisms in the gap. Rothberg *et al* further disclose the rolling circle probe has the added advantage of allowing isothermal amplification to generate thousands of copies of the target nucleic acid.

Assuming, for the sake of discussion, the above characterization of Rothberg is accurate, the Rothberg reference fails to address the deficiencies in Lee as previously explained. Therefore the proposed combination cannot teach each limitation of Applicants' invention and accordingly cannot render Applicants invention obvious.

Specifically, nothing in Rothberg suggests or teaches Applicants' limitation regarding the "signal on" configuration of Applicants' claimed invention. Therefore, Applicants respectfully submit that the proposed combination of Lee with Rothberg fails to teach or suggest all of Applicants claim limitations. Accordingly, Applicants respectfully request the instant rejection be withdrawn.

Claims 1 and 14-15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lee *et al.*, (PCT Publication No. WO 01/40511 A2, published 7 June 2001) in view of Hashimoto (U.S. Patent Application Publication No. US 2001/0024788 Al, issued 27 September 2001). The Office concedes that Lee *et al* are silent with respect to gold electrodes. The Office proposes combination of Lee with Hashimoto to introduce gold electrodes. This rejection is respectfully traversed.

As Applicants have previously explained, Lee fails to teach Applicants' probes configured in a "signal on" configuration and immobilized to an electrode. Regardless of gold electrodes, Hashimoto fails to disclose or suggest Applicants' immobilized probes on an electrode in a "signal on" configuration. Therefore, as the proposed combination fails to teach one or more limitations of Applicants' invention, the proposed combination cannot render Applicants' claimed invention obvious. Accordingly, Applicants respectfully request the instant rejection be withdrawn.

Claims 25, 28-32 and 34 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lee *et al.*, (PCT Publication No. WO 01/40511 A2, published 7 June 2001) in view of Lizardi *et al.*, (U.S. Patent No. 5,312,728, issued 17 May 1994).

The Office alleges that Lee *et al* disclose the internal structure of the intervening second region as having a loop wherein the target binds, and concedes that Lee *et al* do not teach any further internal structure of the second region. The Office proposes combining Lee with Lizardi to allegedly introduce a detectable ribozyme structure that is a loop structure, believed by the Office to be taught by Lizardi.

Applicants respectfully disagree.

Claim 25 requires the immobilized probe comprise first, second and third regions, where the second region is intermediate to the first and third regions. The first region is immobilized upon or approximate to the electrode; the third region is bound to a redox moiety. The second region comprises nucleotides sequences that self hybridize so that in the absence of target hybridization a first loop is formed and in the presence of hybridization a second loop is formed. The first loop positions the redox moiety at a first distance from the electrode, while the second loop positions the redox moiety at a second distance from the electrode. The first and second distance five rise to distinguishable redox events detectable by the electrode, wherein the second distance is closer to the electrode than the first distance. Thus, in the presence of target-probe hybridization, signal is increased relative to the absence of target-probe hybridization. Thus, claim 25 requires the immobilized probe be provided on the electrode in a "signal on" configuration.

An exemplary embodiment encompassed by claim 25 is illustrated in Fig. 2 of the instant application:

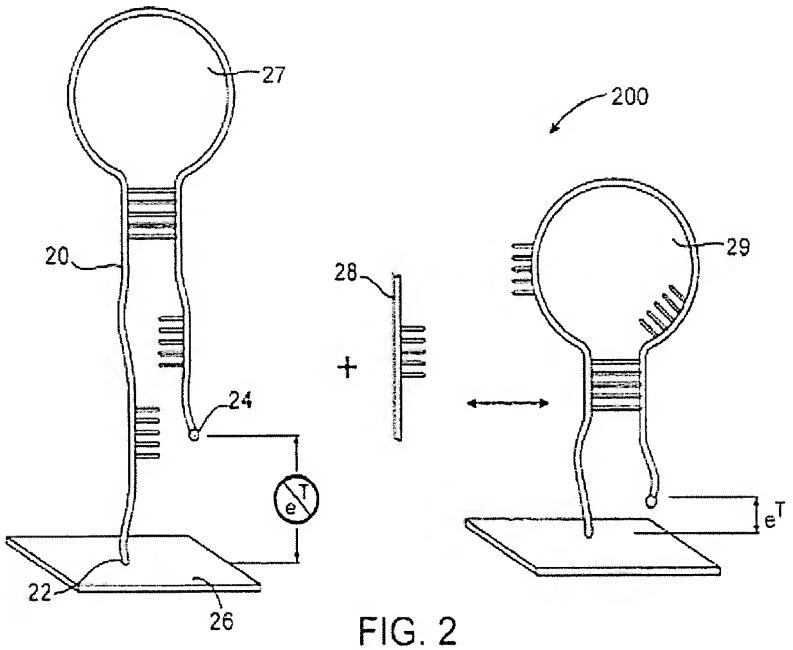

FIG. 2

In order to arrive at the invention, the ordinarily skilled artisan must:

- rely upon the sole disclosure in Lee relating to probe immobilization, namely:

> Depending on the nature of the assay being studied and the detection means being employed, the probe may either be free in solution or immobilized on a support, for instance on an electrode.
>
> Lee at p. 13, line 36 et seq.

- modify the probe of Lizardi to include at least one redox moiety;
- provide for immobilization of the modified Lizardi probe on an electrode; and to provide for the "signal on" configuration required by claim 25

As explained above, *inter alia*, Lee fails to teach each and every limitation of Applicants' claimed invention. Lee in particular fails to disclose how to immobilize a probe to an electrode, and particularly fails to disclose immobilization of a probe to an electrode in a "signal on" configuration. Lizardi does not address the identified deficiencies of Lee, therefore the combination as proposed fails to reach Applicants' invention and render it obvious. Accordingly, Applicants respectfully request the instant rejection be withdrawn.

Applicants further note that the alleged motivation for combining Lizardi and Lee is inadequate. The Office Action asserts that one would combine Lizardi with Lee in order to obtain exponential replication of target polynucleotide to produce up to a billion copies of a single target. However, Lee already asserts single molecule sensitivity via exponential replication of the target polynucleotide to produce up to a billion copies of a single target molecule (See, e.g., p.5, lines 1-10, and p.12, lines 22-26). Applicants respectfully submit that if the suggested motivation to combine the references already exists in each of the references standing alone, the only motivation for suggesting the combination in the present circumstances is to attempt to reach Applicants' invention through impermissible hindsight using Applicants' invention as a template for

construction. Such motivation is improper, and when identified it is appropriate to withdraw the resulting rejection.

Claim 33 is rejected under 35 U.S.C. 103(a) as being unpatentable over Lee *et al.*, (PCT Publication No. WO 01/40511 A2, published 7 June 2001) in view of Lizardi *et al.*, (U.S. Patent No. 5,312,728, issued 17 May 1994) as applied to claim 32 above, and further in view of Hashimoto (U.S. Patent Application Publication No. US 2001/0024788 Al, issued 27 September 2001).

The Office concedes that neither Lee *et al* nor Lizardi *et al* teach gold electrodes, and seeks to fill this gap with the gold electrodes disclosed in Hashimoto. This rejection is respectfully traversed.

Claim 33 ultimately depends from claim 25, and thus incorporates all limitations of claim 25. As Applicants have previously explained, none of the cited references teach or suggest all elements of the detector of claim 25. Hashimoto fails to cure any of the deficiencies discussed above. Therefore the suggested combination of Lee, Lizardi and Hashimoto fails to render Applicants' claimed invention obvious, as the combined disclosures do not disclose or suggest all elements of claim 33, particularly with respect to a detector comprising a probe immobilized in a "signal on" configuration.

Accordingly, Applicants request the instant rejection be withdrawn.

CONCLUSION

Applicants submit that all of the claims are in condition for allowance, which action is requested. Applicants have amended claims withdrawn as a consequence of the earlier restriction requirement to provide the limitations of the currently prosecuted claims. Accordingly, Applicants request rejoinder of withdrawn claims pursuant to MPEP §821.04, and examination pursuant to 37 C.F.R. §1.104.

If the Examiner finds that a telephone conference would expedite the prosecution of this application, please telephone the undersigned at the number provided.

The Commissioner is hereby authorized to charge any underpayment of fees associated with this communication, including any necessary fees for extensions of time, or credit any overpayment to Deposit Account No. 50-0815, order number UCSB-510CIP.

Respectfully submitted,
BOZICEVIC, FIELD & FRANCIS LLP

Date: June 4, 2007

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